AUSTRALIAN PRODUCT INFORMATION – TOBRAMYCIN INJECTION (TOBRAMYCIN SULFATE)

1. NAME OF THE MEDICINE

Tobramycin sulfate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tobramycin Injection is a sterile solution containing tobramycin (as tobramycin sulfate) 80 mg/2 mL.

It is a white or almost white powder that is freely soluble in water; very slightly soluble in ethanol (96%); practically insoluble in chloroform and in ether.

Excipient(s) with known effect

- Sodium metabisulfite

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Solution for injection.

Tobramycin Injection is a clear, colourless to pale brown, sterile aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of serious infections of the following type where they are caused by susceptible organisms:

- skin and skin structure infections including burns, bone infections
- gastrointestinal infections including peritonitis
- central nervous system infections including meningitis, septicaemia and neonatal sepsis
- lower respiratory tract infections including pneumonia, bronchopneumonia, and acute bronchitis
- complicated and recurrent urinary tract infections such as pyelonephritis and cystitis

Aminoglycosides, including tobramycin, should not be used in uncomplicated initial episodes of urinary tract infection unless the causative organisms are not susceptible to other less toxic antibiotics.

Tobramycin can be used in serious staphylococcal infections for which penicillin or other less toxic drugs are contraindicated and where susceptibility testing and clinical judgement indicate its use. If susceptibility tests show a resistance to tobramycin in the causative organisms other appropriate therapy should be instituted.

Note that bacterial cultures should be obtained before and during treatment to isolate and identify etiologic organisms and to test their susceptibility to tobramycin. If the organisms are resistant, other appropriate therapy should be instituted. In patients in whom Gram-negative septicaemia, neonatal sepsis or meningitis is suspected, including those in whom concurrent therapy with a penicillin or cephalosporin and an aminoglycoside may be indicated, tobramycin therapy may be initiated before results of susceptibility studies are obtained. The decision to continue tobramycin therapy should be based upon the results of susceptibility studies, the severity of infection and the important additional concepts discussed below.

4.2 Dose and method of administration

Dosage

Tobramycin Injection may be given intravenously (IV) or intramuscularly (IM) and in either case the dosage is the same. It is desirable to measure both peak and trough serum levels during treatment (see Section 4.4 Special warnings and precautions for use).

Prior to administration, the patient's body weight should be measured for the correct calculation of dosage. In obese patients, the appropriate dose can be calculated by assuming body weight to be the patient's estimated lean body weight plus 40% of the excess.

The usual duration of treatment is 7 – 10 days. A longer duration of treatment may be necessary in complicated infections but should always be combined with renal, auditory and vestibular monitoring. Neurotoxicity is more likely to occur when treatment is for more than 10 days.

Adults (dosage in patients with normal renal function)

For serious infections: 3 mg/kg/day in three doses given every eight hours in equal doses.

For mild to moderate urinary tract infections: 2 – 3 mg/kg/day in two or three equally divided doses.

Life threatening infections: Up to 5 mg/kg/day in 3 or 4 equal doses with reduction to 3 mg/kg/day as soon as clinically indicated. Doses should never exceed 5 mg/kg/day unless serum levels are monitored.

The following table should be used as a guide:

Table 1 - Dosage Schedule Guide for Adults with Normal Renal Function (dosage at eight hour intervals)

Patient bodyweight (kg)	Dose every eight hours			
	Usual dose for serious infections 1 mg/kg every 8 hours (total 3 mg/kg/day)		Maximum dose for life threatening infections (reduce as soon as possible) 1.66 mg/kg every 8 hours (total 5 mg/kg/day)	
	mg	mL	mg	mL

120	120	3.0	200	5.0
110	110	2.75	183	4.5
100	100	2.5	166	4.2
90	90	2.25	150	3.75
80	80	2.0	133	3.3
70	70	1.75	116	2.9
60	60	1.5	100	2.5
50	50	1.25	83	2.1
40	40	1.0	66	1.6

Children and infants

Tobramycin Injection may be given intravenously or intramuscularly in paediatrics.

Children and older infants: 6 – 7.5 mg/kg/day in 3 or 4 equally divided doses (as an example, 2 – 2.5 mg/kg every eight hours or 1.5 – 1.89 mg/kg every six hours).

Neonates (one week of age or less): up to 4 mg/kg/day may be administered in two equal doses every 12 hours.

Dosage adjustment

Renal impairment

Serum tobramycin concentrations should be monitored during therapy. A loading dose of 1 mg/kg is usually given and following that, subsequent doses should be reduced using one of the following regimes: lower the doses or increase the time interval between doses. Both regimes are only guides to be used when serum levels of drug cannot be monitored. They are based on creatinine clearance or serum creatinine level because these levels correlate with the half-life of tobramycin. Neither regime should be used when dialysis is being performed.

Regimen 1: Reduced dosage at eight hour intervals.

An appropriate reduced dosage range can be found in Table 2 for any patient for whom the creatinine clearance or serum creatinine values are known. The choice of dose within the specified range depends on the severity of infection, the susceptibility of the pathogen and the individual patient considerations, especially renal function.

An alternative rough guide for determining reduced dosage at eight hour intervals (for patients whose steady state serum creatinine values are known) is to divide the recommended dose by the patient's serum creatinine (expressed as mg %).

Regimen 2: Prolonged intervals between fixed doses.

Recommended intervals between doses are given in Table 2. The dosage frequency in hours can be determined by multiplying the patient's serum creatinine level (expressed as mg %) by six.

The dosage schedule derived from either method should be used in conjunction with careful laboratory observations of the patient and should be modified as necessary.

Table 2 - Two Maintenance Regimens Based on Renal Function and Body Weight Following a Loading Dose of 1 mg/kg*

Renal function**	Regimen I	Regimen II

Serum creatinine		Creatinine clearance mL/min	Adjusted doses at 8 hour intervals		Adjusted intervals between fixed dose	
mg %	mmol/L		50 – 60 kg	60 – 80 kg	Fixed dose for 50 – 60 kg = 60 mg	Fixed dose for 60 – 80 kg = 80 mg
< 1.4	< 0.12	> 69	60mg	80mg	8 h	8 h
1.4 – 1.9	0.12 – 0.17	69 – 40	30 – 60 mg	50 – 80 mg	12 h	12 h
2.0 – 3.3	0.18 – 0.29	39 – 20	20 – 25 mg	30 – 45 mg	18 h	18 h
3.4 – 5.3	0.30 – 0.46	19 – 10	10 – 18 mg	15 – 24 mg	24 h	24 h
5.4 – 7.5	0.47 – 0.66	9 – 5	5 – 9 mg	7 – 12 mg		
> 7.5	> 0.66	< 5	2.5 – 4.5 mg	3.5 – 6 mg		

*For life threatening infections, dosages 50% above those recommended may be used. Dosage should be reduced as soon as possible after an improvement is noted.

**If used to estimate the degree of renal impairment, serum creatinine concentrations should reflect a steady state of azotaemia.

Method of administration

As a general guide, care should be taken to avoid peak levels greater than 12 µg/mL and trough levels greater than 3 µg/mL. Treatment period should not usually exceed 10 – 14 days. A useful guideline would be to perform serum level assays after two or three doses, so that the dosage could be adjusted if necessary, and also at three to four day intervals during therapy. In the event of changing renal function, more frequent serum levels should be obtained and the dosage or dosage interval adjusted.

In order to measure the peak level, a serum sample should be drawn about 30 minutes after completion of the intravenous infusion or one hour after an intramuscular injection. Trough levels are measured by obtaining serum samples eight hours after the dose or just prior to the next dose of tobramycin. These suggested time intervals are intended only as guidelines and may vary according to institutional practices. These serum-level assays may be especially useful for monitoring the treatment of severely ill patients with changing renal function or of those infected with less sensitive organisms or those receiving maximum dosage.

Each ampoule is for use in a single patient on one occasion only.

Dilution and admixture

For IV administration, the prescribed dose of tobramycin must be diluted in 100 – 200 mL of sterile normal saline or 5% glucose in water for injections. The concentration of tobramycin in the solution should not exceed 1 mg/mL. The diluted solution usually should be infused over a period of 20 to 60 minutes. Infusion periods of less than 20 minutes are not recommended, because peak serum levels may exceed 12 µg/mL.

Tobramycin Injection must not be mixed with other drugs, but should be administered separately according to recommended dose and route (see Section 4.5 Interactions with other medicines and other forms of interactions and Section 6.2 Incompatibilities). In order to reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2 – 8°C for not more than 24 hours.

4.3 Contraindications

Known hypersensitivity to tobramycin or any of the ingredients.

Previous toxic reactions (ototoxicity, nephrotoxicity) or hypersensitivity to aminoglycosides because of the known cross-sensitivity of patients to drugs in this class.

4.4 Special warnings and precautions for use

Clostridium difficile-associated disease

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including tobramycin. A toxin produced with *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

Nephrotoxicity and ototoxicity

As with other aminoglycosides, patients treated with tobramycin should be kept under close clinical observation because of its inherent potential to cause ototoxicity and nephrotoxicity.

Ototoxicity: Tobramycin is prone to cause eighth cranial nerve damage, both vestibular and auditory ototoxicity may occur with high, prolonged, set levels of the drug.

The auditory changes are usually irreversible, usually bilateral and may be partial or total. The risk of aminoglycoside induced hearing loss increases with the degree of exposure to either high peak or high trough serum concentrations.

During therapy, some patients who develop cochlear damage may not show symptoms that warn of eighth cranial nerve damage, and partial or total bilateral damage may continue to develop even after therapy has been discontinued, therefore eighth nerve function should be carefully monitored. Serial audiograms should be obtained in patients that are old enough to be tested. Other manifestations of neurotoxicity include numbness, skin tingling, muscle twitching and convulsions.

Nephrotoxicity: Renal function should be closely monitored, especially in patients who develop signs of dysfunction during therapy.

Tobramycin is selectively concentrated in renal cortical cells and it produces changes in proximal tubules. The drug causes renal impairment characterised by excretion of casts, oliguria, proteinuria and a progressive rise in blood urea and serum creatinine values.

Serum creatinine and creatinine clearance, serum calcium, magnesium, potassium, sodium levels and blood urea nitrogen should also be monitored. For urine, specific gravity and excretion of protein, cells and casts should be observed.

Aminoglycoside induced nephrotoxicity is usually reversible. Rarely, nephrotoxicity may not manifest until the first few days after cessation of therapy.

Use in impaired renal, vestibular and/or auditory function

Evidence of impairment in renal, vestibular and/or auditory function requires discontinuation of the drug or at least reduction in dose if continuation of therapy is considered essential.

In high risk patients, the serum concentration of tobramycin should be monitored closely. Prolonged concentrations above 12 µg/mL should be avoided. Rising trough levels above 2 µg/mL may indicate accumulation of the drug in tissues. It is this accumulation, high peak concentrations, advanced age, dehydration and cumulative doses, which may contribute to ototoxicity and nephrotoxicity. Ototoxicity may occur with peak levels lower than 12 µg/mL (for advice on monitoring levels see Section 4.2 Dose and method of administration).

In patients in whom renal impairment is known or who develop signs of dysfunction during therapy, renal and eighth cranial nerve function should be monitored closely.

Use in the elderly

Elderly patients may have a reduced renal function and therefore it is important that renal function is monitored in such patients. As routine screening tests (such as blood urea nitrogen or serum creatinine) may not show reduced renal function, a creatinine clearance may be more useful.

Paediatric use

Tobramycin sulfate should be used with caution in premature and neonatal infants because of their renal immaturity and the resulting prolongation of serum half-life of the drug. In neonates, infants and children, dosage reductions may be necessary to avoid toxicity. Eighth cranial nerve toxicity should also be monitored.

Use in patients with muscular disorders

Aminoglycosides should be used with caution in patients suffering from muscular disorders such as myasthenia gravis or Parkinsonism, as these drugs may aggravate muscle weakness because of its potential curare-like effect on neuromuscular function.

Use in burn patients

In patients who have extensive burns, pharmacokinetics may be altered resulting in reduced serum levels of tobramycin. Dosage should therefore be based on measured serum levels in these patients.

Use during anaesthesia

Neuromuscular blockade and respiratory paralysis have been reported in cats receiving very high doses of tobramycin (40 mg/kg). The possibility of prolonged or secondary apnoea should be considered if the drug is administered to anaesthetised patients who are concurrently receiving neuromuscular blocking agents such as suxamethonium (succinylcholine), tubocurarine or decamethonium (see Section 4.5 Interactions with other medicines and other forms of interactions). This also applies to patients who are receiving massive transfusions of citrated blood. If neuromuscular blockade occurs, it may be reversed by the administration of calcium salts.

Allergic reactions

Administration of tobramycin may result in allergic reaction. Cross-allergenicity among aminoglycosides has also been known to occur.

Other

Tobramycin Injection contains sodium metabisulfite, which may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than non-asthmatic people.

Therapy with tobramycin may result in overgrowth of non-susceptible organisms. If overgrowth of non-susceptible organisms occurs, appropriate therapy should be initiated.

Although not indicated for local irrigation or application, aminoglycosides administered in this fashion may be absorbed in significant quantities from body surfaces and may cause neurotoxicity and nephrotoxicity. In addition, there have been reports of macular necrosis following intraocular and/or subconjunctival injection of aminoglycosides including tobramycin.

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

Potent diuretics: Etacrynic acid, furosemide (frusemide) and other potent diuretics may cause ototoxicity themselves, or they may enhance the toxicity of tobramycin by altering antibiotic concentrations in serum and tissue.

Other neurotoxic and/or nephrotoxic agents: The concurrent or sequential use of other neurotoxic and/or nephrotoxic drugs may enhance neurotoxicity or nephrotoxicity of tobramycin. This includes other aminoglycosides and cephalosporins, particularly neomycin, streptomycin, kanamycin, gentamicin, paromomycin, viomycin, vancomycin, amikacin and cefaloridine, as well as polymyxin B, colistin and cisplatin.

β-lactam antibiotics: Inactivation of tobramycin and other aminoglycosides has been demonstrated *in vitro* with beta-lactam antibiotics (penicillins and cephalosporins). This has also occurred in patients with severe renal impairment. This inactivation has not been found in patients with normal renal function who have been given the drugs by separate routes of administration.

Skeletal muscle relaxants: Enhanced neuromuscular blockade and respiratory paralysis may occur if tobramycin is given in conjunction with skeletal muscle relaxants such as suxamethonium, tubocurarine or decamethonium. This should be treated with calcium infusions.

Other: Amphotericin B may produce renal toxicity by synergism. Methoxyflurane may produce additive or synergistic nephrotoxicity. Renal impairment may appear at lower than usual dosage levels of the drug.

4.6 Fertility, pregnancy and lactation

Effects on fertility

See section 4.6 Fertility, pregnancy and lactation: Use in pregnancy.

Use in pregnancy – Pregnancy Category D

Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

Aminoglycosides, including tobramycin, cross the placental membrane producing fetal serum levels 25 to 50% of those found in maternal serum. There is evidence of selective uptake of aminoglycosides by the fetal kidney resulting in damage (probably reversible) to immature nephrons. Eighth cranial nerve damage has also been reported following *in utero* exposure to some of the aminoglycosides. Because of their chemical similarity, all aminoglycosides must be considered potentially nephrotoxic and ototoxic to the fetus. It should also be noted that therapeutic blood concentrations in the mother do not equate with safety for the fetus.

The daily subcutaneous administration of tobramycin doses as great as 100 mg/kg to rats had no adverse effect on fertility or reproduction, nor did it affect fetal development. Daily subcutaneous doses of 20 – 40 mg/kg to pregnant rabbits caused anorexia, weight loss, and renal injury. Fifteen percent of the animals of the 20 mg/kg group and 85 percent of those of the 40 mg/kg group died or aborted. Fetal development appeared normal in these animals at the time of death or abortion. No drug-related abnormalities were noted in any of the progeny, despite the maternal toxicity.

There have been several reports of total irreversible bilateral congenital deafness in children whose mothers received streptomycin during pregnancy.

Use in lactation

Tobramycin is excreted in the breast milk with concentrations of 0.60 and 0.85 µg/mL at one and eight hours after an intramuscular dose of 80 mg. Because of the potential risk to the newborn it is recommended that breastfeeding be discontinued during therapy.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (undesirable effects)

As with other aminoglycosides, ototoxicity and nephrotoxicity can occur. The risk of adverse effects is increased in patients with poor renal function, the elderly, patients on prolonged treatment or with serious underlying pathology.

More common adverse reactions include:

Otic: Ototoxicity occurs as the drug penetrates into the inner ear during periods of high serum concentration. Both auditory and vestibular branches of the eighth cranial nerve may be adversely affected. Ototoxicity initially manifests as vestibular dysfunction with or without loss of high-tone activity, similar to that of other aminoglycosides. Symptoms include dizziness, vertigo, tinnitus, roaring in the ears and hearing loss. Hearing loss is usually irreversible. Ototoxic damage may progress in some patients even after the drug is discontinued.

Renal: Patients with pre-existing renal impairment who are treated for longer periods or with higher doses than those recommended are at greater risk. Nephrotoxicity manifests as changes in renal function: rising serum urea, blood urea nitrogen (BUN), nonprotein nitrogen (NPN) and serum creatinine and by oliguria, cylindruria and increased proteinuria. Nephrotoxicity may be increased by the concurrent administration of other drugs (see Section 4.5 Interactions with other medicines and other forms of interactions). Patients with pre-existing renal impairment are at greatest risk. Adverse renal effects can occur in patients with initially normal renal function.

Gastrointestinal: Nausea, vomiting and diarrhoea.

Less common reactions:

Musculoskeletal: The aminoglycosides are known to possess neuromuscular blocking effects and to be capable of exacerbating impairment of neuromuscular transmission in clinical conditions such as myasthenia gravis or severe hypocalcaemia, or when used in conjunction with nondepolarising neuromuscular relaxants such as d-tubocurarine.

Neuromuscular blockade may result in weakness of skeletal muscles and respiratory depression especially in patients with myasthenia gravis, severe hypocalcaemia or who have recently received other neuromuscular blocking agents. Peritoneal lavage with tobramycin could precipitate apnoea because high concentrations of drug come in contact with the diaphragm. Rarely, blockade has been observed following intramuscular or intravenous injection. Tobramycin is usually safely used prior to surgery if given in recommended single doses.

Dermatological: Maculopapular rash, urticaria, itching.

Rare reactions:

Biochemical abnormalities: Some patients with malignant diseases have developed a complex metabolic syndrome of 2 – 8 weeks duration after administration of tobramycin, including hypocalcaemia, hypomagnesaemia, hypokalaemia, hypoalbuminaemia, hypophosphataemia and hypouricaemia. Other reported abnormalities include increased aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum bilirubin and alkaline phosphatase.

Haematological and reticulo-endothelial: Anaemia, granulocytopenia and thrombocytopenia; eosinophilia, decreased platelet and white cell counts.

Immunological: Fever, rash, itching, urticaria. Adverse effects on the immune response via inhibition of chemotaxis and microbicidal activity of phagocytes have been reported. Angioedema, exfoliative dermatitis, stomatitis and anaphylaxis are hypersensitivity reactions reported with aminoglycosides in general.

Neurological: Lethargy. Acute brain syndrome has been reported in an elderly patient after four days of therapy with tobramycin. The delirium was reversed after drug discontinuance. Neurotoxicity is rare with tobramycin. Peripheral neuropathy, paraesthesia and muscle weakness have been reported.

Other: Pain after intramuscular administration and thrombophlebitis after intravenous administration.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

Signs and symptoms: The severity of the signs and symptoms following a tobramycin overdose are dependent on the dose administered, the patient's renal function, state of hydration and age and whether or not other medications with similar toxicities are being administered concurrently. Toxicity may occur in patients treated more than 10 days, given more than 5 mg/kg/day, children given more than 7.5 mg/kg/day, or patients with reduced renal function whose dose has not been appropriately adjusted.

Nephrotoxicity following the parenteral administration of an aminoglycoside is most closely related to the area under the curve of the serum concentration versus time graph. Nephrotoxicity is more likely if trough blood concentrations fail to fall below 2 µg/mL and is also proportional to the average blood concentration. Patients who are elderly, have abnormal renal function, are receiving other nephrotoxic drugs, or are volume depleted are at greater risk for developing acute tubular necrosis. Auditory and vestibular toxicities have been associated with aminoglycoside overdose and occur in patients treated longer than 10 days, patients with abnormal renal function, dehydrated patients and patients receiving medications with additive auditory toxicities. These patients may not have signs or symptoms or may experience dizziness, tinnitus, vertigo, and a loss of high-tone acuity as ototoxicity progresses. Ototoxicity signs and symptoms may not begin to occur until long after the drug has been discontinued.

Neuromuscular blockade or respiratory paralysis may occur following administration of aminoglycosides. Neuromuscular blockade, prolonged respiratory paralysis, and respiratory failure may occur more commonly in patients with myasthenia gravis or Parkinson's disease. Prolonged respiratory paralysis may also occur in patients receiving decamethonium, tubocurarine, or suxamethonium. If neuromuscular blockade occurs, it may be reversed by the administration of calcium salts but controlled or assisted ventilation may be necessary.

Treatment: In managing overdose, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in the patient.

The initial intervention in a tobramycin overdose is to establish an airway and ensure oxygenation and ventilation. Resuscitative measures should be initiated promptly if respiratory paralysis occurs.

Patients that have received an overdose of tobramycin and have normal renal function should be adequately hydrated to maintain a urine output of 3 – 5 mL/kg/hr. Fluid balance, creatinine clearance, and tobramycin plasma levels should be carefully monitored until the serum tobramycin level falls below 2 µg/mL.

Patients in whom the elimination half-life is greater than 2 hours or whose renal function is abnormal may require more aggressive therapy. In such patients, haemodialysis may be beneficial.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Class: Aminoglycoside antibiotic.

Microbiology

Tobramycin has bactericidal activity against many Gram-negative aerobes and against some strains of staphylococci. Aminoglycosides are taken up into sensitive bacterial cells by an active transport process that is inhibited in anaerobic, acidic or hyperosmolar environments. Within the bacterial cell aminoglycosides bind primarily to the 30S ribosomal subunit, inhibiting protein synthesis and generating errors in the transcription of the genetic code. The manner in which cell death is brought about is not fully elucidated.

Tobramycin is usually active against most strains of the following organisms: *Escherichia coli*, *Proteus* species (indole-positive and indole-negative) including *Proteus mirabilis*, *Proteus morganii*, *Proteus rettgeri* and *Proteus vulgaris*; Klebsiella, Enterobacter, Serratia species; Providencia species and Citrobacter species; Staphylococci, including *Staphylococci aureus* (coagulase positive and coagulase negative).

Tobramycin is considered to be more active than most other aminoglycosides against *Pseudomonas aeruginosa* and less active against *Serratia*.

Aminoglycosides have a low order of activity against most Gram-positive organisms; enterococci and streptococci are insensitive.

Aminoglycosides exhibit synergy with antibiotics, such as beta-lactams and vancomycin, which affect the bacterial cell wall and enhance aminoglycoside penetration. *In vitro* studies have shown that an aminoglycoside combined with an antibiotic that interferes with cell wall synthesis affects some group D streptococcal strains synergistically. The combination of benzylpenicillin and tobramycin results in a synergistic bactericidal effect *in vitro* against certain strains of *S. faecalis*. However, this combination is not synergistic against other closely related organisms, e.g. *S. faecium*. Speciation of group D *Streptococci* alone cannot, therefore, be used to predict susceptibility. Susceptibility testing and tests for antibiotic synergism are recommended.

Anaerobic organisms, yeasts and fungi are resistant to aminoglycosides.

Cross-resistance between aminoglycosides occurs and depends largely on inactivation by bacterial enzymes.

Susceptibility Tests

Dilution or diffusion techniques – either quantitative (MIC) or breakpoint should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small-uncontrolled technical factors from causing major discrepancies in interpretation.

A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

Absorption

In adults with normal renal function, a single intramuscular injection of 1 mg/kg body weight will produce peak plasma levels of about 4 µg/mL within 30 – 90 minutes. Serum concentrations can be measured for as long as eight hours. Following intravenous infusion over one hour, the serum concentrations achieved are similar to those obtained after intramuscular administration. Tobramycin is poorly absorbed from the gastrointestinal tract.

Distribution

Tobramycin has been detected in body fluids such as sputum, peritoneal fluid, synovial fluid and abscess fluids following intravenous administration but only low concentrations are found in the cerebrospinal fluid even in the presence of meningeal inflammation. Low concentrations are found in the bile and stools suggesting that biliary excretion is minimal.

Tobramycin accumulates in the kidney, where it is selectively concentrated in renal cortical cells. The half-life of tobramycin in renal tissue is about 74 h.

Tobramycin does cross the placental membranes and is excreted in breast milk.

Metabolism and Excretion

Aminoglycosides do not appear to be metabolised and are excreted virtually unchanged in the urine by glomerular filtration. Practically no serum protein binding occurs. Renal clearance is similar to that of endogenous creatinine. In patients with normal renal function, up to 84% of the dose is recoverable from the urine in eight hours and up to 93% in 24 hours. The serum half-life is usually 2 – 3 hours in adults with normal renal function but in patients with impaired renal function a range from 5 to 70 hours has been reported. Adjustments in the frequency of administration of tobramycin are necessary to allow for the degree of renal impairment. In infants, an average plasma elimination half-life of 4.6 hours has been reported for full-term infants and an average of 8.7 hours for low birth-weight infants.

Peak urine concentrations ranging from 75 to 100 µg/mL have been observed after the intramuscular injection of a single dose of 1 mg/kg. After several days of treatment, the amount of tobramycin excreted in the urine approaches the daily amount administered. When renal function is impaired, excretion of tobramycin is slowed and accumulation of the drug may cause toxic blood levels. In patients undergoing dialysis, 25 to 70% of the administered dose may be removed, depending on the duration and type of dialysis.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Disodium edetate
- Phenol
- Sulfuric acid 40% v/v
- Sodium hydroxide
- Sodium metabisulfite
- Water for injections

6.2 Incompatibilities

Tobramycin injections have been reported to be physically or chemically incompatible with solutions of the following: alcohol 5% in dextrose 5%, cefamandole naftate, clindamycin phosphate and heparin sodium. As a general rule, tobramycin injections should not be mixed with other drugs but should be administered separately according to the recommended dose and route.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C and protect from light. Single use only. Discard unused portion. Unopened ampoules will be suitable for use for up to 6 months after the foil sachet is opened, if replaced in the carton and protected from light.

6.5 Nature and contents of container

Tobramycin Injection 80 mg/2 mL is supplied in five single use Steriluer® ampoules, wrapped in a laminated, LLDPE foil sachet.

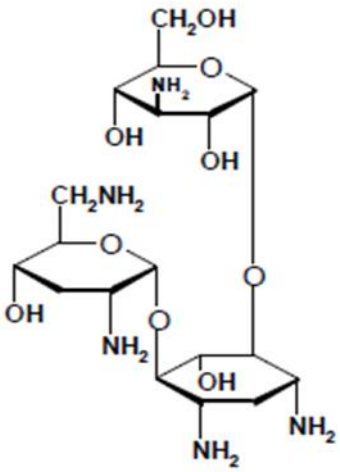
6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Tobramycin is *O*-3-amino-3-deoxy-α-D-glucopyranosyl-(1→6)-*O*-[2,6-diamino-2,3,6-trideoxy-α-D-*ribo*-hexopyranosyl-(1→4)]-2-deoxy-D-streptamine, an antimicrobial substance produced by *Streptomyces tenebrarius*.

Chemical structure



Molecular formula: $C_{18}H_{37}N_5O_9$

Molecular weight: 467.5

CAS number

32986-56-4

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizer.com.au

9. DATE OF FIRST APPROVAL

28 April 2004.

10. DATE OF REVISION

11 December 2019

® Registered trademark

Summary Table of Changes

Section changed	Summary of new information
All	All sections reformatted in line with the new form. Minor editorial changes.
2	Addition of excipient with known effect in line with new form.
3	Addition of dosage form.
4.4	Addition of safety information related to CDAD.
8	Update to Sponsor details including address.